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Structural Basis of DNA Bridging by Barrier-to-Autointegration Factor

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ABSTRACT: Barrier-to-autointegration factor (BAF) is a host cell protein that plays a crucial role in retroviral integration. Preintegration complexes (PICs) stripped of BAF lose their normal integration activity, which can be restored by incubation with purified BAF. BAF bridges double-stranded DNA both intra- and intermolecularly in a non-sequence-specific manner, leading to the formation of a nucleoprotein network. BAF also binds to the nuclear protein lamina-associated polypeptide 2 (LAP2), and is localized with chromatin during interphase and mitosis. The crystal structure of homodimeric human BAF has been determined to 1.9 Å resolution. The fold of the BAF monomer resembles that of the second domain of RuvA. This comparison revealed the presence of the helix-hairpin-helix (HhH) nonspecific DNA binding motif within BAF. A novel feature of BAF's HhH motif is the occupation of the metal binding site by the epsilon-amino group of Lys 6, providing an alternative means of sequestering positive charge. Mutational analysis corroborates the HhH motif's prominent role in DNA binding and argues against a previously proposed helix-turn-helix (HTH) binding site located in another region of the monomer. A model of BAF bridging DNA via the HhH motif is proposed.